The circadian period length is associated with depressive disorders in adolescence

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Tiivistelmä – Referat – Abstract

Tavoitteet. Tässä tutkimuksessa oli tavoitteena selvittää, onko sirkadiaanisen jakson pituus yhteydessä mielialahäiriöihin nuoruudessa. Myöhäisemmän kronotyypin on havaittu olevan yhteydessä useisiin epäsuotuisiin tekijöihin, kuten heikompaan mielenterveyteen. Aiemmissa tutkimuksissa on havaittu, että kronotyypit näyttävät todellisuudessa kuvaavan sirkadiaanisen jakson pituuden poikkeamaa 24 tunnin jaksosta eivätkä niinkään eroavaisuuksia unen ajoittumisessa. Tässä tutkimuksessa tutkimuskysymykset olivat: Onko sirkadiaanisen jakson pituus yhteydessä masennus- ja/ tai ahdistushäiriöiden esiintymiseen 16-19-vuotiailla nuorilla? Muuntaako sukupuoli sirkadiaanisen jakson ja mielialahäiriöiden välistä yhteyttä 16-19-vuotiailla nuorilla? Hypoteesina oli, että 24 tunnista poikkeava sirkadiaanisen jakson pituus olisi yhteydessä masennus- ja/ tai ahdistushäiriöiden esiintymiseen.

Menetelmät. Tämä tutkimus oli osa SleepHelsinki! –tutkimusprojektia, joka on väestöpohjainen kohorttitutkimus ja koostuu kahdesta vaiheesta. Ensimmäisessä vaiheessa 7539 suomea puhuvaa 16-17-vuotiasta nuorta kutsuttiin osallistumaan internet-kyselyyn liittyen terveyskäyttäytymiseen ja uneen. 1411 kyselyyn vastanneesta 329 kutsuttiin tutkimuksen toiseen osaan, jossa arvioitiin osallistujien psykiatrisia häiriöitä MINI-haastattelulla ja mitattiin ihon lämpötilaa sirkadiaanisen jakson pituuden arvioimiseksi. Tutkimuksen lopullinen otos oli 258 nuorta. Tilastollisessa analyysissä käytettiin binaarista logistista regressiota.

Tulokset ja johtopäätökset. Naissukupuoli oli yhteydessä sekä masennus- että ahdistushäiriön korkeampaan esiintymiseen nuorilla. Tutkimuksen tulokset osoittivat, että sukupuoli ja sirkadiaanisen jakson pituus ovat yhteydessä masennushäiriöön nuoruudessa. Sirkadiaanisen jakson pituus ei ollut yhteydessä ahdistushäiriön ilmenemiseen, eikä ikä ollut yhteydessä masennus- tai ahdistuneisuushäiriöihin. Sekä lyhyempi että pidempi sirkadiaaninen jakso olivat yhteydessä masennushäiriön esiintymiseen nuoruudessa.

Avainsanat – Nyckelord – Keywords
sirkadiaaninen jakso, mielialahäiriöt, masennushäiriö, ahdistushäiriö, nuoret

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Tiivistelmä – Referat – Abstract

Aims of the study. The aim of this study was to examine the association of the circadian period length and mood disorders in adolescents. The late chronotype has been associated with a few adversities, such as poorer mental health. In previous studies, it has also been shown that chronotypes might be due to deviations from the 24 hours circadian period length rather than differences in timing of sleep. The research questions of this study were: Is the length of circadian period associated with depressive and/ or anxiety disorders in 16-19-year-olds? Does gender moderate the association between circadian period length and mood disorders in 16-19-year-olds? The hypothesis was that circadian period significantly longer or shorter than 24 hours is associated with a higher risk of depressive and/ or anxiety disorders.

Methods. The study was part of the SleepHelsinki! research project which is a population-based cohort study that consisted of two phases. In the first phase 7539 Finnish speaking adolescents, aged 16-17 were invited to participate in an online survey about health behaviours and sleep. Of the 1411 adolescents participating in the online survey, 329 were invited to the second phase of the study to assess psychiatric disorders of the participants with MINI interview and record the information about their distal skin temperature to assess the length of the circadian period. Information of 258 participants were used in this study. Binary logistic regression was used in the statistical analysis of the data.

Results and conclusions. Female gender was associated with a higher prevalence of anxiety and depressive disorders. The results showed that gender and the length of the circadian period were associated with depressive disorders in adolescence. No association was found between circadian period length and anxiety disorders. Age was not associated with either depressive or anxiety disorders. Both the longer and shorter circadian period and female gender were associated with the occurrence of depressive disorders.

Avainsanat – Nyckelord – Keywords
circadian period, mood disorders, adolecence, depressive disorder, anxiety disorder

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1 INTRODUCTION

It has been presented that adolescents need slightly more than 9 hours of sleep (Carskadon et al., 1980). Even though sleep is highly important for adolescents, it is exceedingly common that adolescents do not get enough sleep or sleep poorly. In a large Finnish study, it was found that about 9 % of 16-17-year-olds have insomnia related symptoms (Kronholm et al., 2015). Similar results are seen globally: a large meta-analysis that reviewed adolescents' sleep patterns worldwide found that more than half the adolescents get insufficient amount of sleep on weekdays as they sleep less than 8 hours per night (Gradisar, Gardner, & Dohnt, 2011). These findings are alarming, as inadequate amount of sleep comes with many adversities.

The duration and regularity of sleep are both associated with well-being and academic performance of adolescents. A later bedtime, which is an indicator of irregular sleep schedules, is associated with poorer academic performance (Cohen-Zion & Shiloh, 2018). This may be related to daytime tiredness, as adolescents who have poorer quality of sleep are less alert at daytime (Short, Gradisar, Lack, & Wright, 2013). Tiredness is associated with lower grades in adolescents (Kronholm et al., 2015) and shorter duration of sleep is associated with poorer executive functions in early adulthood (Kuula et al., 2018). On the other hand, better sleep quality is considered to have a positive effect on school functioning in children, for example increasing achievement motivation (Meijer, Habekothé, & Van Den Wittenboer, 2000) and is directly associated with better academic performance (Adelantado-Renau et al., 2019). Poorer sleep quality is also associated with lower mood (Short et al., 2013). Insomnia symptoms in adolescents are associated with generally poorer mental health and emotional and behavioural problems (Li et al., 2018). As it seems, shorter duration and poorer quality of sleep are associated with a few adversities regarding the daily life of adolescents whereas getting enough sleep and better quality of sleep have positive effects. Besides affecting the daily life of adolescents, sleep disturbances at the age of 16 also predict sleep disturbances later in life (Dregan & Armstrong, 2010).

Furthermore, insufficient sleep and poor sleep quality are associated with health risks and mortality. Short duration of sleep significantly declines life expectancy and increases important health outcomes including diabetes, cardiovascular disease and coronary disease (Itani, Jike, Watanabe, & Kaneita, 2016). The decreased life expectancy associated with short sleep might be partially explained by inflammatory markers (Hall et al., 2015). Poorer sleep quality is also shown to be associated with increased metabolic risk factors whereas sufficient amount of sleep is associated with decreased metabolic risk factors in adolescents (Pulido-Arjona et al., 2018).

1.1. Regulation of sleep-wake cycle

Sleep regulation can be explained by the two-process model according to which sleep is regulated by two distinct processes: a sleep-dependent process and a circadian process (Borbély, 1982). The sleep-dependent process regulates rapid eye movement sleep (REM sleep) and non-REM sleep and explains the variations in sleep propensity due to sleep onset and waking time. After waking, slow wave activity increases and then declines during sleep. This means that sleep propensity increases gradually after waking up. The circadian process in turn accounts for the rhythmic variations in sleepiness that are regulated by the circadian oscillator (Borbély, 1982).

The daily rhythm of sleep and wake times follows a biologic circadian rhythm which is approximately 24 hours. This is referred to as a circadian period. The circadian rhythm is generated by the suprachiasmatic nucleus in hypothalamus (Buijs & Kalsbeek, 2001). The circadian rhythm is intrinsic and maintained even under conditions where there are no environmental cues about the time of the day. As the intrinsic circadian period is not exactly 24 hours some adjustments need to be made every day by the suprachiasmatic nucleus (Stratmann & Schibler, 2006). The intrinsic circadian period is synchronised to the external time by using environmental cues of which light is the most important stimulus (Stratmann & Schibler, 2006).

Changes in the body temperature also follow an approximately 24-hour circadian rhythm. The core body temperature decreases at night and increases during the day (Cuesta, Boudreau, Cermakian, & Boivin, 2017). Distal temperature follows the opposite cycle: the

skin temperature is higher during the day and decreases at night, reaching its peak about one hour before the core body temperature minimum (Cuesta et al., 2017). Here we focus on distal temperature as wrist temperature is used as a measurement of circadian period in this study.

The daily average temperature is somewhat lower in adults than in children (Pronina & Rybakov, 2011). In adolescence the amplitude of body temperature decreases in boys and increases in girls (Pronina, Orlova, & Rybakov, 2015; Pronina & Rybakov, 2011). The body temperature follows a close to 24-hour rhythm and has two peak times in a day, before noon a more prominent one and a somewhat lower one in the evening (Pronina et al., 2015) the minimum temperature occurring usually early in the morning.

1.2. Individual variation in the circadian rhythm

People differ in their sleep-wake cycles both in duration of sleep and timing of sleep. Some individuals' sleep-wake cycle follows a circadian rhythm significantly longer or shorter than 24 hours. This has been demonstrated in prior research, for example in a study performed on delayed sleep phase disorder patients, where it was observed that the circadian period of delayed sleep phase disorder patients was about 30 minutes longer than of good sleepers (Micic et al., 2013). There is also a sleep disorder referred to as a non-24-hour sleep disorder (Zee, Attarian, & Videnovic, 2013), in which individuals follow a rhythm which is usually a somewhat longer than 24 hours. As a result, the sleep onset time shifts to a later time every day or earlier each day in case of a circadian period shorter than 24 hours (Zee et al., 2013).

The length of the circadian period varies between different ethnicities and genders. For example, the length of circadian period is shorter in African-Americans than European-Americans, being 24.07 hours on average for African-Americans and 24.33 hours for European-Americans (Eastman, Tomaka, & Crowley, 2017; Eastman, Molina, Dziepak, & Smith, 2012). Previous studies also indicate that the circadian period is significantly shorter for women than for men and women are more likely to have a circadian period shorter than 24 hours compared to men (Duffy et al., 2011).

1.2.1 Chronotypes

The individual differences in timing of sleep are usually referred to as chronotypes. Chronotypes are often assessed by self-report questionnaires and are usually differentiated by the mid-point of sleep, early chronotypes having mid-point of sleep at an earlier time than late chronotypes. The timing of sleep and duration of sleep are independent traits (Roenneberg et al., 2007). However, it seems that later chronotypes have more insomnia symptoms than earlier chronotypes (Li et al., 2018). Based on a study that examined chronotypes in adolescents it seems that later chronotypes are more likely to be female (Li et al., 2018). This is however contradictory to the finding of a meta-analysis reviewing studies that were mostly focused on adults, where it was found that females on average were an earlier chronotype than males (Randler, 2007).

The late chronotype is associated with a few negative effects on academic performance and health. For example, the late chronotype is associated with poorer grades and poorer day-time alertness (Short et al., 2013), and higher stress levels compared to earlier chronotypes (Haraszti et al., 2014). Individuals with a later chronotype are also more likely to have several unhealthy habits such as poorer adherence to a healthy diet (Maukonen et al., 2016), lower frequency of physical exercise (Haraszti et al., 2014) and more frequent alcohol consumption (Nakade, Takeuchi, Kurotani, & Harada, 2009). Moreover, the later chronotype appears to be associated with more frequent insomnia symptoms (Li et al., 2018).

Even though the timing of sleep is correlated with the individual chronotype, the duration of sleep varies according to social schedule and particularly the work or school schedule. Chronotypes have great differences in duration of sleep when assessed during work and free days (Roenneberg, Wirz-Justice, & Merrow, 2003). During workdays, late chronotypes' sleep onset time is on average two hours later than early chronotypes' despite of similar waking times (Roenneberg et al., 2003). As a result, late chronotypes accumulate a larger amount of sleep debt during workdays (Roenneberg et al., 2003). Sleep duration also differs in all chronotypes between work and free days: duration of sleep on free days is on average one hour longer than on workdays (Roenneberg et al., 2003).

Timing of sleep is normally distributed in all age groups, but on both work and free days there are differences in the midpoints of sleep between and within age groups (Roenneberg et al., 2003). The timing of sleep shifts later in adolescence due to behavioural factors and developmental changes in the circadian timing system (Crowley, Acebo, & Carskadon, 2006). Adolescents have the largest differences in timing of sleep between work and free days as evidenced by the midpoint of sleep. On average, the midpoint of sleep is three hours later on free days than on work or school days in adolescence, whereas in adults the difference is only one hour on average (Roenneberg et al., 2003).

From these results it can be concluded that many adolescents and adults have to shift their sleep between the workdays and the free days. The discrepancy between preferred sleep time and the sleep time on work or school days is referred to as social jet lag (Wittmann, Dinich, Merrow, & Roenneberg, 2006). It is defined as the difference between the midpoints of sleep on work or school nights and free nights. Social jet lag is usually largest among shift workers and it is modulated by the chronotype: late chronotypes sleep less the days when they have morning shifts and the early chronotypes sleep slightly less when they have evening shifts (Juda, Vetter, & Roenneberg, 2013). Social jet lag is more pronounced in late chronotypes, since in the society both school and work usually require earlier waking than would be natural to late chronotypes (Roenneberg et al., 2007). Living in the North also shifts sleep phase later on population level (Borisenkov, 2010). Social jet lag is indeed quite common in higher latitudes (Polugrudov et al., 2016).

1.3. Sleep and mood

Mood disorders are relatively common in adolescence. According to previous studies the lifetime prevalence of depression for adolescents varies from 7,4 to 21,4 % (Lewinsohn, Rohde, & Seeley, 1998; Olsson & Knorring, 1999; Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015) and the prevalence of anxiety disorders from 13,5 to 31,9 % (Merikangas et al., 2010; Essau, Lewinsohn, Olaya, & Seeley, 2014; Essau, Conradt, & Petermann, 2000). Mood disorders appear to be more common among girls than boys: lifetime prevalence of depression varied from 10,7 to 28,6 % for girls and 2,8 – 11,6 % for boys (Lewinsohn et al., 1998; Olsson & Knorring, 1999; Avenevoli et al., 2015). Likewise, the anxiety disorders appear to be almost twice more common among adolescent girls than boys (Merikangas et

al., 2010; Essau et al., 2000). Prior research largely confirms that the mood disorders and psychological wellbeing in general are associated with sleep patterns and problems (Shanahan, Copeland, Angold, Bondy, & Costello, 2014; Roberts & Duong, 2017; Johnson, Roth, & Breslau, 2006). In the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013) sleep problems are symptoms both in anxiety and depressive disorders.

The amount and quality of sleep affect mood and psychological wellbeing. (Shanahan et al., 2014; Roberts & Duong, 2017). The association has been found to be effective the other way around as well: mood disorders can predict sleep problems (Johnson et al., 2006). Short duration of sleep in adolescence has been associated with more emotional and behavioural problems, including depressive symptoms, anxiety and norm-breaking behaviour (Bauducco, Flink, Jansson-Fröjmark, & Linton, 2016). In one longitudinal study, it was found that sleep problems predict and are predicted by several psychiatric disorders, including depressive and anxiety disorders (Shanahan et al., 2014). In addition, in a meta-analysis of longitudinal studies examining the association of insomnia and depression, it was found that insomnia increases the risk of depressive disorders (Baglioni et al., 2011). These results suggest that sleep patterns do play an important role in predicting mood disorders.

Short duration of sleep is shown to predict anxiety, but not the other way around: anxiety does not predict shorter duration of sleep (Roberts & Duong, 2017). In a research exploring the direction of association of insomnia and depressive and anxiety disorders among adolescents, it was found that in 73 % of the comorbid cases anxiety preceded insomnia and in 69 % of the cases insomnia preceded depression (Johnson et al., 2006). However, prior insomnia did not significantly predict anxiety disorders (Johnson et al., 2006). Considering these results, it appears that the association of sleep problems is different for anxiety and depressive disorders and is less clear for anxiety disorders.

Chronotype's association with mood has been vastly studied and the late chronotype is considered to be associated with several disadvantages regarding mental health. Late chronotype is associated with lower psychological wellbeing, for example depressed mood (Bauducco, Richardson, & Gradisar, 2020; Short et al., 2013) and vulnerability to depression

(Antypa et al., 2017). The late chronotype is associated with diagnosed depressive and anxiety disorders even when sociodemographic factors were adjusted for (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2016). Studies examining the genetic factors of chronotypes and mood disorders have reported that the late chronotype and mood disorder symptoms share some genetic basis (Jankowski & Dmitrzak-Weglarz, 2017; Chong, Ptáček, & Fu, 2012).

Furthermore, in adolescence the late chronotype is associated with more behavioural and emotional problems (Li et al., 2018). Girls with late chronotype are more likely to have internalising problems than boys with late chronotype whereas both genders with late chronotypes have a higher risk for externalising problems (Li et al., 2018). Besides the late chronotype being associated with poorer mental health, the difference between the timing of circadian rhythm and social schedule also is associated with mood disorders as social jet lag is associated with higher risk of depression (Polugrudov et al., 2016; Levandovski et al., 2011).

It has been suggested that the people who appear to have a later chronotype do in fact have a circadian period that is longer than 24 hours, resulting in later bedtimes each day (Micic et al., 2013). In a few studies examining the circadian period length on later chronotypes and delayed sleep phase disorder patients it has been found that later chronotypes (Lack, Bailey, Lovato, & Wright, 2009) and delayed sleep phase disorder patients (Campbell & Murphy, 2007) do indeed have a longer circadian period compared to earlier chronotypes or healthy controls. This would mean that the factors associated with chronotypes would actually be associated with the intrinsic circadian period length rather than individual differences in the timing of sleep. While the academic community has extensively explored chronotypes' associations on mood disorders, there is still a shortage of studies examining the association of non-24-hour circadian period and mental health. As sufficient sleep is essential for adolescents' academic performance not to mention physical and mental health and can have far-reaching outcomes, it is important to study the associations of circadian period length in adolescence.

1.4. Research questions

The aim of this study was to examine the association between the circadian period length and mood disorders in adolescents. The research questions of this study are:

1) Is the length of circadian period associated with depressive and/ or anxiety disorders in 16-19-year-olds?
2) Does gender moderate the association between circadian period length and depressive and/ or anxiety disorders in 16-19-year-olds?

We hypothesised that a circadian period significantly longer or shorter than 24 hours would be associated with higher risk of depressive and/ or anxiety disorders in adolescents. The gender was hypothesised to moderate the association between circadian period length as the circadian period length is different for females and males. As males appear to have a longer circadian period than females, it was hypothesised that the association of circadian period length and mood disorders would be stronger for males than females.

2 METHODS

2.1. Procedure

The data in this study are part of the Sleep Helsinki! study of the Sleep and Mind Research Group at the University of Helsinki. Sleep Helsinki! is a population-based cohort study and the aim of the project is to produce new information regarding sleep and sleep disturbances in adolescents and to develop new evidence-based methods to improve and prevent the sleep problems or difficulties managing healthy sleep rhythm. In the first phase of the study, the information about sleep, health and behaviour was gathered in the online survey. The second phase of the study, used in the current analyses, consisted of distal temperature measurements and the MINI-interview on the psychiatric symptoms.

2.2. Participants

Information about adolescents aged 16-17 years in Helsinki for the study was gathered from Digital and Population Data Services Agency in September 2016. Of all the adolescents living in Helsinki and born between 1999 and 2000 (n= 10 476) all Finnish speaking were invited to participate in the study (n= 7539). 3 789 of them were born in 1999 and 3 750 in 2000, 50 % of them being girls. A total of 1 411 adolescents participated in the online survey of which a few had to be excluded due to technical difficulties related to the survey and in the end 1 374 were included in the study (18% of the invited 7 539). Regardless that majority of respondents were girls (66 %), the mean age of the participants did not differ from the mean age of the initial cohort (p=.34). Following this, 552 participants were invited to the second phase of the study which 329 completed. Some of the participants had to be excluded from the current study due to inaccurate measurements and as a result, measurements of 258 adolescents (18% of the phase 2 participants, 74 % girls) were used in the analyses of this study. The final sample of this study was 258 adolescents aged 16–19 years (mean=17.47, standard deviation = .68, range 15.90–18.91).

2.3. Circadian period length

The length of the circadian period was measured by using distal skin temperature measurements from wrist. Wrist temperature can be non-invasively measured using a wireless temperature system. In this study Thermochron iButton was used. iButton is a reliable way to measure skin temperature for long periods of time with a user-friendly software (van Marken Lichtenbelt, Wouter D et al., 2006).

Two variables were used for the circadian period length: the circadian period length deviation from 24 hours and the deviation squared. The deviation of the length of the circadian period was calculated as the difference of the circadian period length from 24 hours. The deviation squared was included to analyse the associations between both shorter and longer circadian period lengths and mood disorders.

2.4. Psychiatric disorders

Psychiatric disorders were assessed using Mini-International Neuropsychiatric Interview (MINI), which is a short, structured interview. MINI contains 120 questions and can be used to assess 17 axis I DSM-IV disorders and 24 current and lifetime diagnoses in axis I along with suicidality and antisocial personality disorder (Sheehan et al., 1997). MINI has two to four questions per disorder plus additional symptom questions that are only used if the screening questions derive a positive answer. It has the same reliability and validity as SCID-P, which a structural clinical interview for DSM-III disorders, but administration of MINI interview takes significantly less time (Sheehan et al., 1997), hence it fitted well for purposes of this study.

The versions used in this study were 6.0.0 and 7.0.1. With the 6th version DSM-IV and ICD-10 disorders can be assessed and with the 7th version DSM-5 and ICD-10 disorder can be assessed. The 6.0.0 version was used in the start of the study but after the 7.0.1 version was released it replaced the older version in assessing the psychiatric disorders in the study. The versions differ slightly in the diagnostic criteria of some of the disorders.

The psychiatric disorders assessed by MINI that were included in this study were the depressive and anxiety disorders. Considering the depressive disorders, the past and current depressive disorders were combined. In the analyses of the anxiety disorders the following disorders were combined: past and current social anxiety disorder, generalised anxiety disorder, panic disorder, obsessive compulsive disorder, social phobia and agora phobia.

2.2. Statistical Analysis

The software used in the statistical analyses was the IBM SPSS 25. The association of circadian period length and mood disorders was analysed using binary logistic regression analysis. In the analysis as the explanatory variable both the deviation of circadian period length and the deviation of circadian period length squared were used. The squared variable was used to examine if the association of the circadian period length and mood disorders was nonlinear as it was assumed that circadian period both shorter and longer than 24 hours would be associated with the occurrence of mood disorders. The analyses were

performed for depressive and anxiety disorders separately. The goodness of fit if the model was analysed using the Hosmer-Lemeshow test. Gender and age were adjusted for in the logistic regression models.

3 RESULTS

1.1. Participant description

There were more females (74.0 %) than males in the study sample. Mood disorders were fairly common among adolescents. A total of 178 participants (69,0 %) had either a current or past depression or anxiety disorder diagnosis. Both anxiety and depressive disorders were more common among females than males: 53,8 % of the girls had either an anxiety or depression disorder and 28,4 % of the boys had either anxiety or depressive disorder. Depression was more common than anxiety disorders within both genders. The distribution of depression and anxiety disorders among participants is shown in Table 1.

Table 1. The distribution of mood disorders among participants.

	All		Female		Male	
Mood disorders	N	%	N	%	N	%
Depression	112	43.1	94	49.2	18	26.9
Anxiety	65	22.1	56	29.3	9	13.4
Concurrent depression and anxiety	55	21.2	47	24.6	8	11.9

3.2. Circadian period length

The circadian period length varied between 20.32 to 27.88 hours. The mean and range of the circadian period length for both genders and participants with or without a mood disorder diagnosis are shown in Table 2. Adolescents with depression had a circadian period slightly longer than non-depressed participants (Figure 1), but when the means were compared with a t-test the difference was found to be insignificant ($t(258)=-1.86$; $p=.064$). The mean length of circadian period was somewhat shorter for females than males, but the difference was found insignificant when compared with a t-test ($t(258)=-1.17$; $p=.243$).

Table 2. Circadian period length among participants.

Participants	Mean	SD	Range
All	24.19	1.28	20.32-27.88
Female	24.13	1.24	20.32-27.88
Male	24.36	1.41	20.45-27.52
Depressed	24.35	1.08	21.59-27.88
Non-depressed	24.07	1.41	20.32-27.07
Anxious	24.30	1.28	21.83-27.88
Non-anxious	24.16	1.29	20.32-27.56

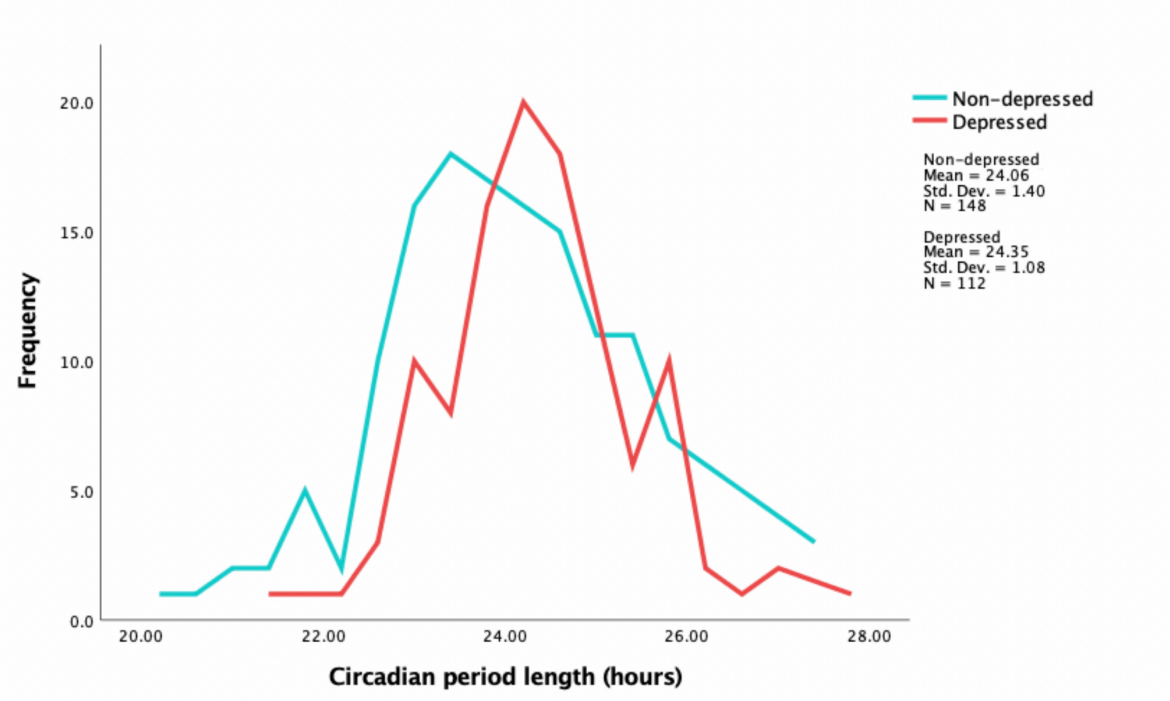

Figure 1. *The circadian period length in depressed and non-depressed adolescents*

3.3. Circadian period and mood disorders

A binary logistic regression analysis was used to assess the association between the circadian period length and past or current anxiety and depressive disorders. The multivariate models that was used to assess the association included gender, age, circadian period length deviation from 24 hours and circadian period length deviation from 24 hours squared as predictors of anxiety and depressive disorders on two separate analyses. The age did not predict the occurrence of anxiety or depressive disorders. No association on past or current anxiety disorders were found for the circadian period length deviation from 24 hours (B=0.11; p=.353) or the circadian period length deviation squared (B=0.01; p=.831)

(Table 3). The gender was independently associated with the occurrence on both anxiety (B=-1.02; p=.010) and depressive disorders (B=-1.02; p=.001).

Table 3. Summary of statistics for the binary logistic regression equation predicting the occurrence of anxiety disorders.

Factor	B	SE	Wald	df	p	OR
Circadian period length deviation from 24 hours	0.11	0.119	0.86	1	.353	1.12
Circadian period length deviation from 24 hours squared	0.01	0.058	0.05	1	.831	1.012
Age	0.01	0.213	0.004	1	.953	1.01
Gender	-1.02	0.396	6.67	1	.010	0.36
Constant	-0.12	3.722	0.001	1	.975	0.89

The circadian period deviation from 24 hours was associated with depressive disorders and the association was statistically significant (B=0.33; p=.009). Likewise, the circadian period length deviation from 24 hours squared was associated with the depressive disorders (B=-1.63; p=.013). The binary logistic regression model statistically significantly predicted the occurrence of past or current depressive disorder in the data [$X^2(4) = 25.83$; p = .000]. The summary of the results of the analysis is shown in Table 4. The model correctly classified 61,4 % of the cases. A Hosmer-Lemeshow goodness-of-fit test was performed to determine how well the data fits the model. The test result indicates that the data fits the model well [$X^2(8) = 7.125$ p = .523].

Table 4. Summary of statistics for the binary logistic regression equation predicting the occurrence of depressive disorders.

Factor	B	SE	Wald	df	p	OR
Circadian period length deviation from 24 hours	0.33	.126	6.87	1	.009	1.39
Circadian period length deviation from 24 hours squared	-1.63	.066	6.11	1	.013	0.85
Age	0.22	0.19	1.25	1	.264	1.241
Gender	-1.02	0.32	10.24	1	.001	0.36
Constant	-2.60	3.37	0.59	1	.44	0.08

3.4. Gender as a moderating factor

To assess if gender moderates the association of circadian period length and depressive disorders, an interaction variable of gender and circadian period length deviation was added to the model. The result show that gender did not moderate the association of circadian period length and depressive disorders (B=0.78; p=.747). As no significant association between circadian period length and anxiety disorders were found, no test was performed to analyse if gender moderates the association on anxiety disorders.

4 DISCUSSION

4.1. Main findings

The aim of this study was to investigate if the circadian period length is associated with mood disorders in adolescence. We found that the circadian period length and gender were associated with depressive disorders. Gender did not moderate the association. Contradictory to the hypothesis, no association between circadian period length and anxiety disorders was found.

The results show that the length of the circadian period is associated with the occurrence of depressive disorders. Participants with shorter or longer circadian period had a higher probability of having a past or current depressive disorder. This supports the hypothesis that both shorter and longer circadian period are associated with depressive disorders. The circadian period for adolescents with past or current depressive disorder was 24 hours 21 minutes on average when for non-depressed adolescents it was 24 hours 4 minutes on average. As discussed earlier, the later chronotype is associated with a few adversities, including higher risk of mood disorders (Antypa et al., 2016). It has been suggested that chronotypes are actually differences in the circadian period length rather than timing of sleep (Micic et al., 2013; Lack et al.,2009). This would indicate that the results of this study are in line with the previous studies demonstrating that late chronotype is associated with depressive disorders (Antypa et al., 2016).

Besides the result that the longer circadian period length was associated with depressive disorders, the association of circadian period length and depressive disorders was nonlinear,

indicating that both the shorter and longer circadian period were associated with depressive disorders. This could be the result of social jet lag, as for both the people with circadian periods significantly shorter or longer than 24 hours, it can be more challenging to adjust to work or school and social schedules, resulting in poorer psychological wellbeing. Based on previous studies social jet lag is associated with depression (Polugrudov et al., 2016; Levandovski et al., 2011). Even though the midpoints of sleep were not studied here, it can be assumed that longer circadian period increases the risk of having more social jet lag as it has been shown that late chronotypes have more social jet lag than earlier chronotypes (Roenneberg et al., 2003). The late chronotype actually indicating a longer circadian period means that people with longer circadian periods would have more social jet lag.

Our results cast new light on the association of sleep problems and mood disorders. The results of this study suggest that it might not be the timing of sleep described as chronotype that is associated with depressive disorders but the length of the intrinsic circadian period. More specifically, both shorter and longer circadian period are associated with a higher risk of having a depressive disorder. The circadian period was approximately 15 minutes longer in adolescents with depressive disorders than non-depressed adolescents. This is consistent with what has been found in previous studies, as the late chronotype is associated with mood disorders and symptoms (Antypa et al., 2016; Bauducco et al. 2020).

Sleep patterns and anxiety symptoms and disorders have been associated in several studies (Antypa et al., 2016; Roberts & Duong, 2017), yet in this study no association between circadian period length and anxiety disorders were found. This could be due to the number of participants with an anxiety disorder being too low for the analysis to have enough statistical power to yield significant results. On the other hand, as shorter duration of sleep has been shown to be connected to anxiety (Antypa et al., 2016); Roberts & Duong, 2017), it could be that the association between sleep problems and anxiety disorders might be due to another factor instead of circadian period length.

The findings of this study also support previous research on gender differences in the circadian period length. It has been shown that females tend to have a shorter circadian rhythm than males (Duffy et al., 2011). In this study the circadian period length for females

was 24.13 on averages whereas it was 24.36 for males on average. The difference was found insignificant when tested with t-test but the means of circadian period lengths for both genders are in line with prior research (Duffy et al., 2011).

The results of this study also show that gender was independently associated with mood disorders, but it does not moderate the association of circadian period length and depressive disorders. Being female was associated with an increased risk of having an anxiety or depressive disorder. In this study it was hypothesised that gender would moderate the association of circadian period length and mood disorders, more specifically that for males the association would be stronger compared to females, but no such interaction was observed. In the sample of this study there were considerably more females than males and notably less mood disorders among males compared to females. The limited number of males with anxiety or depressive disorders in this sample might partially contribute to why the gender was not found to moderate the association of circadian period length and depressive disorders.

The frequency of anxiety disorders in this sample is consistent with the results of previous studies: the total percentage of adolescents in this study with a past or current anxiety disorder was 22,1 % while in prior prevalence studies it has appeared to be between 13,5 and 31,9 % (Merikangas et al., 2010; Essau et al., 2014; Essau et al., 2000). Likewise, the gender difference in prevalence of anxiety disorders was replicated here as in this sample and previously the anxiety disorders are perceived to be almost twice more common in adolescent females than males (Merikangas et al., 2010; Essau et al., 2000). However, the prevalence of depressive disorders in this study was considerably higher compared to previous observations: in this sample the 43,1 % had either a past or current depression whereas in prior research the lifetime prevalence of depressive disorders among adolescents has been between 7,4 and 21,4 % (Lewinsohn et al., 1998; Olsson & Knorring, 1999; Avenevoli et al., 2015). In this study almost half of the females (49,3 %) and about a quarter of males (26,9 %) had a past or current depression disorder. These percentages are likewise considerably higher when compared to previous studies (Lewinsohn et al., 1998; Olsson & Knorring, 1999; Avenevoli, et al., 2015). Nevertheless, the result that depressive

disorders occur more frequently among females than males is consistent with the findings of prior research (Lewinsohn et al., 1998; Olsson & Knorring, 1999; Avenevoli et al., 2015).

The association of circadian period length and depressive disorders can be accounted for by genetic factors. Firstly, it has been shown that genetics explain some of the variation in chronotypes. In recent studies it has been discovered that single-gene mutations account for the extreme early or late chronotypes (Ashbrook, Krystal, Fu, & Ptáček, 2020). Subsequently, several loci have been associated with chronotypes, for example PER2 and PER3 (Jankowski & Dmitrzak-Weglarz, 2017; Ashbrook et al., 2020; Chong et al., 2012).

Secondly, in association studies and candidate gene studies multiple polymorphisms in different loci that affect maintaining or generating the circadian rhythm have found to be associated with mood disorders. People with these polymorphisms tend to have more depressive symptoms (Liberman, Halitjaha, Ay, & Ingram, 2018). Moreover, polymorphisms in genes that are associated with changes in length of circadian rhythm or sleep duration have also been associated with depressive and bipolar symptoms and disorders (Mendoza & Vanotti, 2019). This suggests that genetic factors might account for the association between circadian period length and depressive disorders found in this study.

4.2. Strengths and limitations

The strengths of this study include using validated and objective methods when measuring psychiatric disorders and circadian period length and having moderately large sample. The circadian period length was measured using wireless temperature system Thermocron iButton, which is an objective method to analyse the circadian period length. Additionally, the MINI interview which was used to evaluate psychiatric disorders is a reliable and valid method to accurately assess the occurrence of psychiatric diagnoses. The results of this study were in line with previous studies studying chronotypes. To our knowledge, this was the first study examining the association of circadian period length and psychiatric disorders.

One potential limitation of the study is that the numbers of females and males were uneven in this sample. In addition, mood disorders were less common among males and in this sample, there were very few males with an anxiety disorder. Even though anxiety disorders are quite common in adolescent population, the number of adolescents, especially males, with anxiety in this sample might be too low to yield results. This may be the reason why no association with circadian period length and anxiety disorder was found. Increasing the sample size might lead to finding significant association for anxiety disorders and circadian period length as well. Alternatively, sleep might be associated with anxiety disorders through other factors than the circadian period length.

In future studies, further investigation on association between circadian period length and anxiety disorders is needed. Additionally, it would be important to further examine the association of shorter and longer circadian period length and depressive disorders and if it is mediated by social jet lag or possibly other factors. Future research could also aim to distinguish how much the circadian period length has to differ from 24 hours to increase the risk of depressive disorders.

4.3. Conclusions

The findings of this study support the hypothesis that both shorter and longer circadian periods are associated with depressive disorders in adolescence. One reason for this association might be that it is more challenging for the adolescents with longer circadian period to adjust to the normal school schedule and early mornings and conversely more challenging for adolescents with shorter circadian period to alter their sleep patterns in accordance to social schedules that take part late in the evening. Similar genetic basic might also account for the association of depressive disorders and circadian period length. Until further research, it remains unclear if other mood disorders are also associated with the length of the circadian period.

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